

## The international quality requirements for the conduct of clinical studies and the challenges for study centers to implement them

### Introduction

In the past 15 years, quality guidelines have been developed for the conduct of clinical research. The Good Clinical Practice Guidelines (GCP) published by the International Conference on Harmonization (ICH) have been implemented and become law in some countries. Based on the GCP, regulatory authorities installed national rules for the conduct of clinical studies. Finally, Standard Operating Procedures (SOP) of Pharmaceutical Companies and Clinical Research Organizations (CRO) describe tactical aspects of clinical research. Those tools resulted in an increase in the quality of clinical studies. However, it is crucial for clinical research centers to implement measures that allow the adherence to those guidelines in order to remain competitive.

Cancer patients are increasingly being treated within clinical studies. Thus, it is of particular interest to oncology clinics to qualify as study centers in order to provide their patients with the latest treatment options, to offer them alternatives, and, last but not least, to participate in the global research activities.

Daily practice in clinical research reveals many unresolved problems related to the quality requirements. The GCP and other binding guidelines leave ample space for interpretation with regard to translation of the rules into daily practice. On one hand, this leaves flexibility to researchers; on the other hand, SOPs of their partners (e.g. pharmaceutical companies) create conflicts which have the potential to jeopardize the implementation and constructive conduct of projects.

Because of the lack of a standard source of information and incomplete international harmonization, it is still complicated for an investigator to obtain an overview of the current rules and obligations for the conduct of clinical trials on human subjects. During an extensive literature search in Medline/PubMed in 2003, no articles were found providing a comprehensive summary of the current valid guidelines.

The different regulations of the national regulatory authorities are all based on the GCP of the ICH. But often, because of poor specificity, these guidelines are not able to give completely satisfactory answers to daily practical problems that an investigator may have at a trial site.

In this editorial, we list the most comprehensive guidelines and rules including regulatory demands concerning the quality of the conduct of clinical studies with drugs in the USA and

the European Union (EU). We then discuss the impact of GCP and SOP of Study Sponsor on the clinical research conduct in study centers.

### International ethical principles

The first international instrument on the ethics of medical research, The Nuremberg Code [1], was promulgated in 1947 as a consequence of the trial of physicians who had conducted atrocious experiments on unconsenting prisoners during the Second World War. The Code, designed to protect the integrity of the research subject, set out conditions for the ethical conduct of research involving human subjects, emphasizing their voluntary consent to research.

The Universal Declaration of Human Rights was adopted by the General Assembly of the United Nations in 1948 [2]. To give the Declaration legal as well as moral force, in 1966, the General Assembly adopted the International Covenant on Civil and Political Rights. Article 7 of the Covenant states "... no one shall be subjected without his free consent to medical or scientific experimentation".

The Declaration of Helsinki [3], issued by the World Medical Association in 1964, is the fundamental document in the field of ethics in biomedical research, and has influenced the formulation of international, regional and national legislation and codes of conduct. The Declaration of Helsinki amended several times, most recently in 2000, is a comprehensive international statement of the ethics of research involving human subjects. It sets out ethical guidelines for physicians engaged in both clinical and non-clinical biomedical research.

These three documents may be considered as an historical foundation for today's GCP.

### International guidelines for the conduct of clinical trials

There are three international guidelines in place for the protection of human subjects in clinical trials.

- (i) The World Health Organization (WHO) guidelines for GCP for trials on pharmaceutical products [4].
- (ii) International Ethical Guidelines for Biomedical Research Involving Human Subjects prepared by the Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the WHO [5].
- (iii) The ICH GCP [6].

The WHO has developed their guidelines in order to establish globally applicable standards for the conduct of biomedical research on human subjects. The WHO Good

Clinical Practice guideline was originally prepared in 1991–92 with 15 experts from drug regulatory authorities, academia and the pharmaceutical industry. The proposed guidelines were then circulated for comments to the Member States, to the relevant Expert Working Group of ICH and to the pharmaceutical industry.

It concerns all WHO Member States, but specifically countries where national regulations or requirements do not exist or require supplementation. Their relevant government officials may designate or adopt, in part or in whole, these guidelines as the basis on which clinical trials should be conducted.

The WHO GCP guidelines are addressed to investigators, ethics review committees, pharmaceutical manufacturers and other sponsors of research, monitors, statisticians and drug regulatory authorities.

The CIOMS, an international non-governmental organization in official relations with the WHO founded in 1949, has published in 2002 in collaboration with the WHO their revised/updated international guidelines. The purpose of the CIOMS guidelines is to recommend how the fundamental ethical principles that guide the conduct of biomedical research could be applied to low-resource countries, taking into consideration the cultural and socio-economic circumstances, national laws, and executive and administration arrangements.

The impact of the WHO and CIOMS guidelines is not substantial, because they are not part of the national regulations of the USA and the EU, in contrast to the ICH guidelines.

The ICH GCP was developed within the Expert Working Group of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). The ICH is a joint initiative with experts from the regulatory authorities of Europe, Japan and USA, and from the pharmaceutical industry of the three regions as equal partners. Observers to this conference include experts from the WHO, European Free Trade Association, Canada and Australia. Expert working groups were created to draft guidelines on four main topic areas: quality, safety, efficacy and multidisciplinary. Since the inception of ICH, 37 guidelines covering these topics have been produced. The work under the Efficacy heading is concerned with the design, conduct, safety and reporting of clinical trials. (Table 1 gives a list of relevant ICH Guidances. The ICH guideline ‘Good Clinical Practice: Consolidated Guideline’ (Efficacy6) is widely considered to be one of the major achievements of the early phase of ICH.

Most countries in the EU, as well as other future EU Member States, Switzerland, Japan and the USA, have guidelines and partially legally binding regulations based on GCP.

The objective of this ICH GCP guidance is to provide a unified standard for the EU, Japan and the USA to facilitate the mutual acceptance of clinical data by the regulatory authorities in these jurisdictions. Such harmonization makes human, animal and material resources more economical and eliminates unnecessary delays in the global development and

**Table 1.** List of relevant ICH guidances and topics

Code	Topic
E2A	Clinical Safety Data Management: Definitions and Standards for Expedited Reporting
E2B	Clinical Safety Data Management: Data Elements for Transmission of Individual Case Safety Reports
E3	Structure and Content of Clinical Study Reports
E5	Ethnic Factors in the Acceptability of Foreign Clinical Data
E6	Good Clinical Practice: Consolidated Guidance
E7	Studies in Support of Special Populations: Geriatrics
E8	General Considerations for Clinical Trials
E9	Statistical Considerations in the Design of Clinical Trials
E10	Choice of Control Group in Clinical Trials
M3	Non-clinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals
S6	Safety Studies for Biotechnology-Derived Products

ICH, International Conference on Harmonization.

**Table 2.** Extract of the investigator’s responsibilities according to ICH GCP

The investigator should:
Be a qualified, experienced physician to assume responsibility of the proper conduct of the trial and should provide evidence with up-to-date curriculum vitae.
Be thoroughly familiar with the study medications.
Comply with GCP and the applicable regulatory requirements.
Permit monitoring and auditing by the sponsor and inspection by the regulatory authorities.
Maintain a list of qualified persons with delegated significant trial duties.
Be able to demonstrate a potential for recruiting the required number of subjects.
Have adequate number of qualified and well informed staff to conduct the trial properly and safely.
Be responsible for all trial related medical decisions.
Ensure that adequate medical care is provided to a subject for any adverse events.
Communicate with the IRB/IEC (ethics committee) before initiating a trial and should have written all required written information to be provided to subjects.
Conduct the trial in compliance with the protocol agreed to by the sponsor (signature).

availability of new medicines by maintaining safeguards on quality, safety and efficacy, and regulatory obligations to protect public health [7, 8].

The investigator’s responsibilities are specified quite extensively and Table 2 gives an extract of what an investigator should do according to ICH GCP.

## Regional regulations

### USA

The current regulations for conducting clinical trials with pharmaceutical compounds in the USA can be found in the Code of

Federal Regulations (CFR). The CFR is a codification of the general and permanent rules published in the Federal Register by the Executive departments and agencies of the Federal Government. Title 21 of the CFR is reserved for rules of the Food and Drug Administration (FDA). Each title (or volume) of the CFR is revised once a year. It is available electronically (Table 3).

The FDA is part of the US Department of Health and Human Services. The FDA requirements are the most comprehensive in the world; it has published a large number of guidances. Some of these are simply ICH documents, but the FDA has gone far beyond this, in supplying a large amount of practical information. Their guidances are not binding [9], they represent the agency's current thinking on the topic. An alternative approach may be used if such an approach satisfies the requirements of the applicable statutes and regulations.

The FDA acts as a public health protector by ensuring that all drugs on the market exhibit a high degree of safety and efficacy. Authority to do this comes from the implementation of the 1938 Federal Food, Drug and Cosmetic Act, a law that has undergone many changes over the years.

The US provisions of particular applicability to clinical trials are listed in Table 4.

The Federal Register is a source of information on what FDA or any other government agency is doing. Published daily, the Federal Register carries all proposed and finalized regulations. Furthermore, the FDA has published Information Sheets for Clinical Investigators and Institutional Review Boards. These Information Sheets provide an explanation of the FDA's interpretation of the requirements in clinical trials as they are published in the CFR 21.

All these regulations, information sheets and additional guidelines are available at the official homepage of the FDA, where an investigator can obtain an understanding of the drug development and regulatory process in the USA (see also Table 3).

### European Union

As a result of significant differences that have developed over the years in the national requirements for carrying out clinical trials across the EU, legislation has been introduced in an attempt to simplify and harmonize the administration of clinical trials.

**Table 3.** Important and useful internet websites

ICH homepage	<a href="http://www.ich.org">www.ich.org</a>
EMA—European Medicines Evaluation Agency	<a href="http://www.emea.eu.int">www.emea.eu.int</a>
European Commission Pharmaceuticals Unit	<a href="http://pharmacos.eudra.org">http://pharmacos.eudra.org</a>
Legislation and guidance documents in the EU governing medicinal products	<a href="http://dg3.eudra.org/F2/eudralex/index.htm">http://dg3.eudra.org/F2/eudralex/index.htm</a>
Swiss Agency for Therapeutic Products	<a href="http://www.swissmedic.ch">www.swissmedic.ch</a>
The World Medical Association Declaration of Helsinki (2000 update)	<a href="http://www.wma.net/e/approvedhelsinki.html">www.wma.net/e/approvedhelsinki.html</a>
ICH Guideline for Good Clinical Practice	<a href="http://www.ifpma.org/pdfifpma/e6.pdf">www.ifpma.org/pdfifpma/e6.pdf</a>
World Health Organization	<a href="http://www.who.ch">www.who.ch</a>
<b>Food and Drug Administration (FDA) websites</b>	
FDA homepage	<a href="http://www.fda.gov">www.fda.gov</a>
Guidance documents	<a href="http://www.fda.gov/cder/guidance/index.htm">www.fda.gov/cder/guidance/index.htm</a>
Laws enforced by FDA and CFR 21	<a href="http://www.fda.gov/opacom/laws/default.htm">www.fda.gov/opacom/laws/default.htm</a>
Good Clinical Practice	<a href="http://www.fda.gov/oc/gcp">www.fda.gov/oc/gcp</a>

**Table 4.** Federal regulations essential to the conduct of clinical trials in the USA

Regulation or guideline	Summary of essential content
21 CFR 11: Electronic records; electronic signatures	Controls and requirements for electronic data
21 CFR 50: Protection of Human Subjects	Informed consent requirements
21 CFR 54: Financial Disclosure by Clinical Investigators	Requirements for investigators to disclose financial relationships with sponsors
21 CFR 56: Institutional Review Boards	Requirements for independent review of human research
21 CFR 312: Investigational New Drug Application	Defines the scope of human research under jurisdiction of the FDA; outlines the responsibilities of investigators and sponsors in clinical trials
21 CFR 314: Applications for FDA approval to market a new drug	Procedures and requirements to market a new drug
The ICH GCP Guideline	Published separately as a document in the Federal Register (62 FR 25692)
The FDA Information Sheets for Clinical Investigators and Institutional Review Boards	Provides an explanation of the FDA's interpretation of the requirements in clinical trials

FDA, Food and Drug Administration; ICH GCP, International Conference on Harmonization Good Clinical Practice.

*The EU Directive on GCP in Clinical Trials: Directive 2001/20/EC [10].* The full title of the legislation—‘Directive 2001/20/EC of the European Parliament and of the Council on the Approximation of the Laws, Regulations and Administrative Provisions of the Member States Relating to Implementation of Good Clinical Practice in the Conduct of Clinical Trials on Medicinal Products for Human Use’ explains its primary purpose. Its provisions must come into force in each EU Member State by 1 May 2004. It is therefore the first time that statutory controls have been put in place to define the ways in which clinical trials are carried out.

Directive 2001/20/EC has a particularly wide scope and applies to every clinical trial on medicinal products, whether sponsored by industry, government, research organizations, charity or a university. The Directive sets standards for protecting clinical trials subjects, including incapacitated adults and minors. Importantly, it establishes ethics committees on a legal basis and provides legal status for certain procedures, such as time within which an opinion must be given. It lays down standards for commencing a clinical trial, for the manufacture, import and labeling of investigational medicinal products (IMPs), and provides for quality assurances of clinical trials and IMPs. To ensure compliance with these standards, it requires Member States to set up inspection systems for Good Manufacturing Practice (GMP) and GCP. It also provides guidelines for safety monitoring of patients in trials, and sets out procedures for reporting and recording adverse drug reactions and events. To help with the exchange of information between Member States, secure networks will be established linked to European databases for information about approved clinical trials and pharmacovigilance.

All clinical trials on medicinal products for human use should be designed, conducted, recorded and reported according to the principles of good clinical practice. The EU Commission is required to publish detailed guidelines. This guideline, released for consultation on 10 July 2002, clarifies the principles of GCP in the conduct of clinical trials in the EU [11]. It states that sponsors and investigators shall also take into account the existing Community Guidelines, in particular the note for guidance on GCP (CPMP/ICH135/95) [6].

The national competent authorities of the Member States remain responsible for conducting inspection of the sites concerned by any clinical trial conducted to verify compliance with the provisions on GCP and GMP.

The texts of legislation and other provisions governing medicinal products in the European Community can be found on the EudraLex/Pharmaceutical Unit website of the European Commission (Table 3).

**Implication of GCP and Sponsor-SOP on daily clinical research practice**

Academic centers in oncology have the ongoing task of maintaining or improving the quality of medical care of their patients. The benefit of new interventions, however, can only be evaluated by intensive research. Participation in the

conduct of clinical trials is therefore unavoidable. It provides contact with the most recent state of the art research and increases the quality of care of patients. To conduct clinical research in compliance with existing guidelines and national regulatory requirements is a challenge for an Academic Research Center. It is time consuming to obtain an overview of the complex nature of guidelines. The implementation of the current binding rules in the daily practice of a study center requires professional management of clinical trials. The organization and structure of the research staff have to be adjusted to the manifold materia and the growing needs of the particular centers. A responsible research director and departments with well educated staff for the different domains of clinical trials have to be established.

One conclusion of our work is that the ICH GCP and the Declaration of Helsinki, in compliance with the requirements of the national regulatory authorities, should serve as the basis of each clinical trial in order to establish international acceptance of clinical trial data. The guidances published by the FDA are a helpful support concerning the implementation of clinical studies.

What is the impact of these rules on the conduct of clinical trials in daily practice? Patient care is confronted with an increasing degree of bureaucracy topped by the need to keep an eye on the study’s internal procedures. In many cases, the latter is the real problem, namely the room for interpretation of GCP by pharmaceutical companies [12]. The fact that the SOPs are usually constructed in extreme detail, can lead to conflict situations, which impair the practicability of clinical trials in research centers.

Examples for GCP and protocol violations occur for instance, with the patient information and informed consent. Informed consent prospectuses created by the sponsor often contain an enormous amount of information, and are too extensive and incomprehensible for the layman. A clear

**Table 5.** GCP and protocol compliance problems of our research center in daily practice

Excessively lengthy patient information prospectuses.
Definition and interpretation of investigator and subinvestigator. To be an Investigator in a clinical study means among others the completion of several forms. In our opinion, only those doctors who are actively involved in patient information and decision on diagnostic and therapeutic procedures in study patients should be (sub-) investigators. Residents in education shall therefore only become investigators if they are actively and directly involved in the study conduct.
Curriculum vitae (CV) of all hospital staff involved in the study are needed. Resident doctors, who have seen a trial subject once or twice, have to submit a CV or fill out other forms, i.e. financial disclosure. Sometimes CVs of pharmacists or laboratory personal are required without their direct involvement in the study.
Non-uniform handling concerning serious adverse events reporting.
Reimbursement of the standard chemotherapy in a randomized placebo-controlled study.
Data protection and confidentiality related to the transfer of patients’ data to third parties (e.g. CT scans and histology slides for second review).
Rights and obligations of study centers; study agreements.

GCP, good clinical practice guidelines; CT, computed tomography.

and reasonable document with a non-technical language and a length of three or four pages seems to be more appropriate. Further examples of GCP compliance problems are listed in Table 5.

Additional education of the research staff in the EU and the presentation of the FDA guidance could make the necessity for filling out some forms more understandable.

With the implementation of professional structures in research centers with competent manpower that helps to interpret GCP, the necessary competence to not abandon the lack of GCP to the free interpretation by pharmaceutical companies should be achievable. Research centers need to develop their own SOPs in order to set minimum standards.

Some of the problems must be discussed carefully between the concerned study centers, the industry and the competent authorities. Further work on the mutual common interpretation of guidelines for the conduct of clinical studies is needed in order to achieve a high quality standard while maintaining feasibility.

If guidelines are mainly developed by partners who are not conducting the trials on site, then we move into a century of unrealistic theory and will therefore prevent academic research activities.

A. Gajic, R. Herrmann & M. Salzberg\*

University Hospital Basel, Clinical Research Oncology,  
Spitalstrasse 26, CH-4031 Basle, Switzerland  
(\*E-mail: [salzbergm@uhbs.ch](mailto:salzbergm@uhbs.ch))

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